Remarks

The June 17, 2005 Official Action has been carefully reviewed. In view of the amendments submitted herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset it is noted that a shortened statutory response period of three (3) months was set forth in the June 17, 2005 Official Action. Therefore, the initial due date for response was September 17, 2005. A petition for a 2 month extension of the response period is presented with this response, which is being filed within the two month extension period.

At page 2 of the Official Action, the Examiner has objected to claims 65, 66, and 68 for improperly referring to an antecedent in the previous claim. Applicants have followed the Examiner's helpful suggestion and amended the claims to recite "said AT" instead of "(AT)." Accordingly, Applicants respectfully request that the objection be withdrawn.

The Examiner has also rejected claims 56 and 57 under 35 U.S.C. §112, second paragraph for alleged indefiniteness on various grounds.

Claims 70, 71, and 73 have been rejected for allegedly failing to satisfy the written description requirements under 35 U.S.C. §112, first paragraph on various grounds.

The Examiner has rejected claims 54-57, 59, and 63 under 35 U.S.C. §102(b) as allegedly anticipated by Kuhstoss et al. (Gene (1996) 183:231-236).

Lastly, the Examiner has rejected claim 58 under 35 U.S.C. §103(a) as allegedly unpatentable over Kuhstoss et al. and claims 73 and 75 under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent 5,712,146.

The foregoing objection and rejections constitute all of the grounds set forth in the June 17, 2005 Official Action for refusing the present application.

In accordance with this amendment, claims 70, 71, and 73 have been cancelled. Additionally, claims 56, 57, 65, 66, and 68 have been amended. The amendments to claims 56 and 57 are intended to eliminate language perceived by the Examiner to be indefinite. Claims 65, 66, and 68 have been amended to properly refer to an antecedent in a previous claim, as noted hereinabove. New claim 77 is included with the instant amendment. Support for claim 77 can be found, for example, at page 22, line 23 to page 23, line 7.

No new matter has been introduced into this application by reason of any of the amendments presented herewith.

In view of the present amendment and the reasons set forth in this response, Applicants respectfully submit that the objection to claims 65, 66, and 68; the 35 U.S.C. §112, first paragraph rejections of claims 70, 71, and 73; the 35 U.S.C. §112, second paragraph rejections of claims 56 and 57; the 35 U.S.C. §102(b) rejection of claims 54-57, 59, and 63; and the 35 U.S.C. §103(a) rejections of claims 58, 73, and 75, as set forth in the June 17, 2005 Official Action, cannot be maintained. These grounds of rejection are, therefore, respectfully traversed.

CLAIMS 56 AND 57, AS AMENDED, MEET THE REQUIREMENTS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The Examiner has rejected claims 56 and 57 under 35 U.S.C. §112, second paragraph for alleged indefiniteness on the following two grounds.

First, it is the Examiner's position that claim 56 is indefinite for recitation of the phrase "natural extension module." The Examiner contends that the phrase is unclear because "the metes and bounds of *all* naturally occurring allelic variants are unknown" as "what is made via genetic engineering today (outside the scope of the claim) may be found as a naturally occurring allelic variant tomorrow

(inside the scope of the claim)." Applicants respectfully disagree with the Examiner. However, in an effort to eliminate any ambiguity perceived by the Examiner, Applicants have amended claim 56 to recite that "said acyltransferase domain is an extension module acyltransferase domain." Support for this amendment is inherent in the claim language as previously presented and can also be found, for example, at page 16, line 22 through page 17, line 18 and page 18, line 24 through page 19, line 7. Applicants submit that the deletion of the term "natural" from claim 56 eliminates the Examiner's perceived ambiguity as to whether a particular AT domain is encompassed by the claim because of whether the domain was found in nature or made via genetic engineering. Inasmuch as the skilled artisan would understand the metes and bounds of the phrase "an extension module acyltransferase domain," Applicants respectfully submit the instant rejection cannot be reasonably maintained.

Second, the Examiner contends that the metes and bounds of the phrase "produced by mutation" in claim 57 are unclear. Applicants have amended claim 57 to eliminate the allegedly ambiguous phrase. As amended claim 57 recites that the "ketosynthase domain which is the source of said engineered-KSq and said acyltransferase domain occur together in an extension module." In view of this amendment, Applicants respectfully submit that claim 57 cannot reasonably be held to be indefinite.

In light of the foregoing, Applicants submit that the rejections of claims 56 and 57 under 35 U.S.C. §112, second paragraph for alleged indefiniteness are untenable and request their withdrawal.

THE WRITTEN DESCRIPTION REJECTIONS OF CLAIMS 70, 71, AND 73 UNDER 35 U.S.C. §112, FIRST PARAGRAPH HAVE BEEN RENDERED MOOT

The Examiner has maintained the rejection of claims 70, 71, and 73 for allegedly failing to satisfy the written

description requirements under 35 U.S.C. §112, first paragraph on several grounds. It is the Examiner's position that while the specification provides support for extension modules in general, the specification allegedly does not adequately provide support for the specific extension modules recited in claim 71 in combination with a loading module as described in claim 64. Furthermore, the Examiner contends that while the specification supports claims to a polyketide synthase comprising the KSq domain of oleandomycin, the AT2 domain of rapamycin, the ACP domain of DEBS, and the first and second extension modules of DEBS, the specification allegedly does not provide support for any extension module as recited in claim 70. Lastly, the Examiner alleges that the specification fails to adequately describe the monensin loading module recited in claim 73.

Applicants continue to respectfully disagree with the Examiner for the reasons already made of record in the February 22, 2005 Official Action response. However, in the interest of expedited prosecution, Applicants have cancelled claim 70, 71, and 73. Accordingly, the instant rejections have been rendered moot and Applicants respectfully request the instant rejections be withdrawn.

CLAIMS 54-57, 59, AND 63 ARE NOT ANTICIPATED BY KUHSTOSS ET AL.

The Examiner has rejected claims 54-57, 59, and 63 under 35 U.S.C. §102(b) as allegedly anticipated by Kuhstoss et al. (Gene (1996) 183:231-236). Kuhstoss et al. allegedly disclose a hybrid PKS comprising the loading module of the tylosin PKS and the first two extension modules of spiramycin. The Examiner contends that the tylosin loading module contains a KSq domain and an AT domain comprising an arginine in the active site. It is the Examiner's position that the engineered-KSq domain recited in claim 54 reads on the naturally occurring KSq domain of the tylosin loading module

of Kuhstoss et al.

Applicants disagree with the Examiner's position. The Examiner "stresses that the [instantly rejected claims] are product claims, not method claims, and the product of the art need not be produced by the process in the claim so long as said product can be produced whatsoever." However, Applicants respectfully submit that the PKS disclosed by Kuhstoss et al. fails to satisfy all of the recitations of claim 54, from which claims 55-57, 59, and 63 depend. Indeed, item iii) of claim 54 recites that the "engineered-KSq is a ketosynthase (KS) domain which effects decarboxylation of a loaded optionally substituted malonyl, wherein said engineered-KSq domain is obtained by replacing the active site cysteine of a KS domain of an extension module with a glutamine." Accordingly, the KSq domain of the loading module of the instantly claimed PKS is a KS domain from an extension module. The PKS described by Kuhstoss et al. comprises the tylosin loading module and, therefore, comprises a KS domain from a loading module and not an extension module as instantly claimed. Applicants submit that Kuhstoss et al. wholly fail to teach a loading module comprising a KS domain from an extension module as required by claim 54. Inasmuch as Kuhstoss et al. fails to teach each and every limitation of claim 54, Applicants respectfully submit that it cannot be reasonably held that Kuhstoss et al. anticipates the instant claims.

Furthermore, the Examiner states that the instant claims do not "require the KSq of the claim to be recombinant since any KSq having the same features as a "replaced" KSq can be considered." Applicants respectfully disagree. KS domains of extension modules naturally possess an active site cysteine and not a glutamine, as instantly required by claim 54. Inasmuch as the active site cysteine residue of the extension module KS domain must be changed to a glutamine residue, Applicants submit that it **necessarily** follows that the claimed

PKS comprises a recombinant or "engineered" KS domain and not a "natural" KS domain like the KS domain of the tylosin loading module in the PKS described by Kuhstoss et al. Accordingly, the PKS disclosed by Kuhstoss et al. cannot be reasonably held to anticipate the instant claims.

Applicants also submit herewith a phlogeny tree of the ketosynthase domains of polyketide synthases (http://web.libragen.com/Phylogeny/full_ks_tree.jpg). The phylogeny tree clearly demonstrates that natural KSq domains, such as the KS domain from the tylosin loading module taught by Kuhstoss et al., are linked phylogenetically. Furthermore, it is evident that KSq domains have significantly different amino acid and nucleotide sequences than other KS domains, such as KS domains from extension modules, based on their separate grouping on the phylogenic tree. Accordingly, Applicants submit that it is clear that a KS domain from an extension module with an altered active site residue, as instantly claimed, is different than a natural KSq domain from a loading module, such as the KSq domain from the tylosin loading module disclosed by Kuhstoss et al.

In light of the foregoing, Applicants submit that the rejection of claims 54-57, 59, and 63 under 35 U.S.C. §102(b) as allegedly anticipated by Kuhstoss et al. is untenable and respectfully request its withdrawal.

CLAIMS 58, 73, AND 75 ARE NOT RENDERED OBVIOUS BY KUHSTOSS ET AL. OR U.S. PATENT 5,712,146

The Examiner has rejected claim 58 under 35 U.S.C. §103(a) as allegedly unpatentable over Kuhstoss et al. and claims 73 and 75 under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent 5,712,146.

With regard to the rejection of claim 58, the Examiner contends that it would have been obvious to a skilled artisan to perform the "opposite" of the experiment described in Kuhstoss et al. as a "simple proof-of-principle experiment"

resulting in the production of a hybrid PKS comprising the malonyl specific KSq of spiramycin and the first two extension modules of tylosin. Applicants respectfully take exception to the Examiner's position in this regard. At the outset, Applicants note that claim 58 recites that the "**acyltransferase** domain is specific for loading with malonyl." In the instant rejection, however, the Examiner discusses only the use by Kuhstoss et al. of a "malonyl-specific KSq" domain, not an AT domain. Accordingly, Applicants the Examiner's reliance on Khustoss et al. in support of this rejection is misplaced. In any case, Applicants submit that the instant rejection cannot be reasonably maintained for the reasons set forth below.

Rejected claim 58 ultimately depends from claim 54. As stated hereinabove, claim 54 requires that the KSq domain of the loading module be a KS domain from an extension module. In the allegedly obvious "proof-of-principle" experiment described by the Examiner, the resultant hybrid PKS would comprise a loading module with a KSq domain from the spiramycin loading module, not an extension module. Accordingly, the resultant PKS would not have a recombinant loading module and would not, as expressly recited in claim 54, comprise a loading module KSq domain derived from an extension module. Furthermore, Applicants submit that Kuhstoss et al. wholly fail to teach or suggest the use of an extension module KS domain in a loading module. Indeed, Kuhstoss et al. specifically teach at page 235 that the "KS^{Q} domain is unlikely to be involved in substrate choice." Accordingly, Kuhstoss et al. actually provide no incentive for one of ordinary skill in the art to substitute a KSq domain into a loading module for the purpose of loading an optionally substituted malonyl.

It is also the Examiner's position that claims 73 and 75 are unpatentable over the '146 patent. Applicants have cancelled claim 73, as previously noted. Accordingly the

rejection of claim 73 has been rendered moot. The Examiner contends that the '146 patent teaches hybrid PKS enzymes using a combination of "enzymes, modules, active sites or portions thereof" from PKS gene clusters and that "examples of hybrid replacement clusters include clusters with genes derived from ... tylosin ... synthase gene clusters." Applicants respectfully disagree. The instant claim is drawn to a PKS comprising the tylosin loading module and a plurality of extension modules wherein at least the first extension module is not naturally associated with the tylosin loading module. Applicants note that there is no description in the '146 patent of a loading module. Accordingly, while the '146 patent generally discloses combining "enzymes, modules, active sites or portions thereof" from different PKSs and invites further experimentation, there is no teaching or suggestion that it would be desirable to specifically replace loading modules between PKSs. It is a well-settled premise in patent law that "silence in a reference is not a proper substitute for adequate disclosure of facts from which a conclusion of obviousness may justifiably follow". In re Burt, 148 U.S.P.Q. 548 (CCPA 1966). Inasmuch as the '146 patent is silent with regard to the specific swapping of loading modules, Applicants submit that the instant §103 rejection of claim 75 cannot reasonably be maintained.

In light of the foregoing, Applicants submit that the rejections of claims 58, 73, and 75 under 35 U.S.C. §103(a) are untenable and respectfully request their withdrawal.

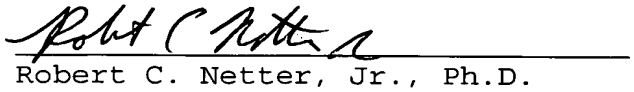
CONCLUSION

In view of the amendments presented herewith and the foregoing remarks, it is respectfully urged that the objection and rejections set forth in the June 17, 2005 Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the

allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number give below.

Respectfully submitted,
DANN, DORFMAN, HERRELL AND SKILLMAN
A Professional Corporation

By 
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